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Case Report

Glomerulonephritis associated with chronic granulomatous disease and systemic lupus erythematosus

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Introduction

Chronic granulomatous disease (CGD) is an inherited immunodeficiency disorder which results from malfunction of the NADPH oxidase system in phagocytic cells. Deficiency of this oxidase, responsible for production of microbicidal oxygen metabolites (e.g. superoxide), leads to reduced killing of catalase-positive bacteria (especially staphylococci) and fungi, and renders affected patients susceptible to recurrent pyogenic infections [1,2]. Granuloma formation is induced by unresolved local bacteria containing foci. Sixty per cent of CGD is inherited as a sex-linked trait due to mutations in the gp 91 phox gene which resides at Xp 21.1. An autosomal recessive inheritance is less frequent [3].

Clinical manifestations start in 80% before the second birthday [4] and consist of recurrent pyoderma, suppurative lymphadenitis, pneumonia, enteritis, liver abscess, osteomyelitis, and failure to thrive. Aspergillus pneumonia is the leading cause of death [5]. Under continuous prophylaxis using intracellularly active antimicrobials the survival rate at age 20 has increased to 50% [4]. This report describes a boy with CGD with an unusual systemic and renal complication, namely lupus erythematosus with diffuse proliferative glomerulonephritis.

Case report

The patient (GD) is the first of two children of non-consanguineous parents. The mother is prone to infections and, as demonstrated by various leukocyte tests (Table 1), is a carrier of the disease, like the sister. The father is healthy. From the age of 10 weeks the patient developed recurrent episodes of enteritis, cervical and inguinal lymphadenitis, otitis, and pneumonia. Studies of the humoral immune system did not show any abnormalities. At 12 months of age testing

of peripheral polymorphonuclear neutrophil cells (PMN) revealed a severe deficiency of superoxide anion production, no staining of PMN exposed to nitroblue tetrazolium, and a reduced cytochrome b concentration (Table 1). RFLP analysis showed a mutation at Xp 21.1 (gp 91 phox). However, the precise molecular genetic mechanism still remains unclear. After diagnosis of CGD, prophylaxis with co-trimoxazole and after an additional year with itraconazole was instituted, which reduced the rate of infections. Nevertheless at the age of 3.7 years a severe Candida pneumonia occurred. Incisor teeth were extracted because of severe caries.

In December 1993 at the age of 5.5 years routine examination revealed slight proteinuria and microhaematuria. Some weeks later severe oedema of the eyelids, hands, and ankles, a butterfly rash, and a discrete maculopapular exanthema on the upper and lower extremities developed. On admission in February 1994 we additionally observed reduced motility and tenderness of the right hip, knees, fingers, and ankles. Weight was 20.4 kg, height 123 cm, and blood pressure 110/70 mmHg. Cervical and submandibular lymph nodes were increased in size but acute infection was absent. Ultrasound examination revealed hepatosplenomegaly and both kidneys appeared large (volume >97th centile) and hyperechogenic. Chest X-ray showed slight interstitial pulmonary infiltration, and echocardiography some thickening of the pericardium. Cranial CT scan was normal.

Laboratory findings

Blood. Hb 9.2 g/dl, leukocytes 4500/µl, CD4/CD8 ratio 0.55 (normal 1–1.4), platelets 40000–100 000/µl, creatinine 0.5 mg/dl, urea 31 mg/dl, total proteins 5.6 decreasing to 4.7 g/dl, albumin 32 decreasing to 23 g/dl, IgA, IgM, and IgG normal, cholesterol 215–345 mg/dl, electrolytes, transaminases and coagulation factors normal.

Serological findings. ANA 1:320 (normal <1:40), ds-DNA (ELISA) 2154 IU/ml (normal <40 IU/ml), ssDNA 98% (normal <20%), ENA (nRNP, SSB) positive, ANCA normal. Functional tests of com-

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Table 1. Function tests of peripheral polymorphonuclear neutrophils (PMN)

Subject	O ₂ ⁻ production (nmol/10 exp 6 PMN/min)	NBT test (%positive cells)	Cytochrome b (pmol/10 exp 6 PMN)	FACS (%positive cells)
Patient	0.031	0	0.16	2.94
Mother	7.640	88	4.30	86.50
Father	14.210	100	5.80	99.16

NBT, nitroblue tetrazolium; FACS, fluorescence-activated cell scan

plement: classical pathway 20%, alternative pathway <20% (normal 80–120%, haemolytic titration assay), C3 0.34 mg/ml (normal 0.5–0.9), C4 0.04 mg/ml (normal 0.1–0.4), C3 Nef negative. Cardiolipin 35 U/ml (normal <25). Viral and fungal antibodies within normal ranges.

Urine. Proteinuria 3.7–6.3 g/m²/24 h (Coomassie method), SDS-PAGE 93% albumin, 2% low-molecular, 5% high-molecular proteins, erythrocytes up to >500/μl, leukocytes 25–60/μl, creatinine clearance 88 ml/min/1.73 m².

Renal biopsy. Diffuse proliferative glomerulonephritis was found in 25 glomeruli with glomerular basement membrane thickening and segmental subendothelial deposits (MPGN-like). PAS staining demonstrated occasional adhesions and immunofluorescence granular deposits of IgA, IgG, IgM, C3, and C3d in the mesangium and along glomerular basement membranes in subendothelial and subepithelial locations.

Clinical course

The patient was treated with prednisone 60 mg/m²/day for 7 weeks followed by decreasing doses on alternate days (Figure 1). In addition, he received frusemide, nifedipine, and atenolol because of rising blood pressure. Antibiotic prophylaxis was continued with rifampicin (15 mg/kg/day), itraconazole (5–10 mg/kg/day) and colistin (3 × 10⁶ U/day). The peripheral oedema and the other clinical symptoms disappeared within a few weeks, the general state improved, and somatic development remained normal. Intercurrent otitis media and lymphadenitis were successfully treated with ampicillin and cefuroxime. Two episodes of upper airway infection subsided spontaneously. No clinical or serological signs of fungal infection appeared.

After 8 months of steroid treatment proteinuria decreased to 0.3–0.9 g/m²/day and serum albumin levels rose to 4.2 g/l. Renal function remained normal (serum creatinine 0.3 mg/dl, urea 22 mg/dl, creatinine clearance 166 ml/min/1.73 m²); Hb increased to 13.2 g/dl, ANA titres decreased to 1:80 and ds-DNA to 282 IU/ml.

Discussion

Involvement of the urinary tract has been reported in 38% of patients with CGD. It consists mainly of urinary tract infections and obstructions due to granu-

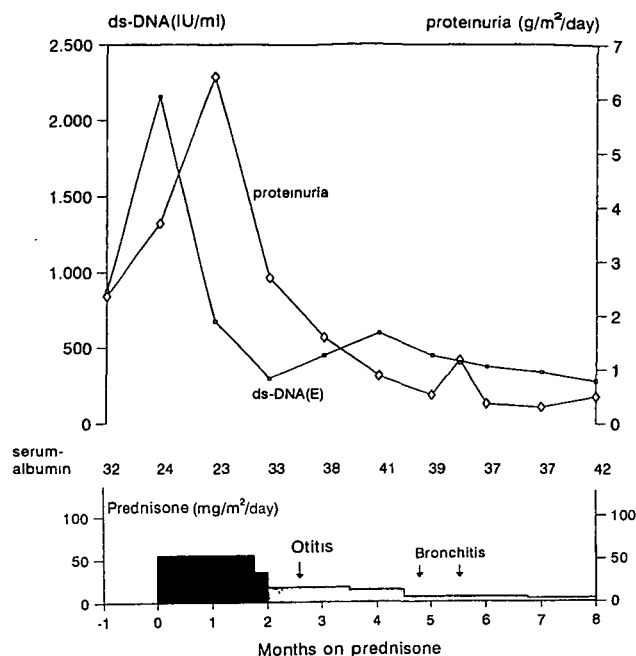


Fig. 1. Course of proteinuria (g/m² body surface/day), serum albumin (g/l) and double-stranded (ds) DNA 1 month before and during 8 months on prednisone therapy. ■ Daily □ Every other day.

loma formation, eventually leading to strictures and renal abscesses [6]. In contrast, glomerular lesions have been described in only six cases of CGD aged 3–18 years [6–10]. The initial features were usually mild, consisting of proteinuria and microscopic haematuria. Renal function was decreased in four cases; two patients required haemodialysis. Our patient is the only one who developed overt nephrotic syndrome with oedema. One further patient reported by Manzi *et al.* [10] exhibited a similar clinical course, also associated with signs and symptoms of SLE.

SLE is a rare disease in small children. According to Cameron *et al.* only 130 children below age 10 with SLE have been reported in the literature; 80% of them initially presented with renal symptoms and 50% developed nephrotic syndrome. Under treatment with corticosteroids and cytotoxic agents the survival rate in this age group has improved to 85% after 10 years [11].

Manifestations of lupus have repeatedly been noted in the family history of CGD patients. Therefore the association of SLE and CGD appears to be causally related. According to Manzi *et al.* [10], 22 female

Table 2. Patients with chronic granulomatous disease and glomerulonephritis

Authors	Age (years), sex	Symptoms	Renal function	Renal biopsy findings	Treatment	Outcome
van Rhenen <i>et al.</i> 1987 [7]	17, f	Subcutaneous abscess P 2.1 g/l, Hm P 0.3	Rapid deterioration anuria (6d) SCR 1.1 GFR 60	Focal GN (advanced sclerosis, crescents) interstitial fibrosis Extramembranous GN with IgG, IgM, C1 deposits	Haemodialysis (210 d) drainage of abscess Rifampicin, sulphafurazole, co-trimoxazole	Recovery of renal function At 10 years P 0.2 g/l, GFR 35 Aspergillus sepsis
Cottin <i>et al.</i> 1982 [8]	5.5, m	Bladder granuloma				Lung infiltration, Aspergillus sepsis, death at 17 years
Frifelt <i>et al.</i> 1985 [9]	12, m	P 1.1, Hm	ESRD at 16 years	At 14 years: focal segmental glomerulosclerosis, tubular atrophy. Autopsy: granulomas in kidney and other organs	Haemodialysis, prednisone, cyclophosphamide, cyclosporin A, amphotericin B	
Manzi <i>et al.</i> 1992 [10]	3, m	SLE, P 2.8 Serum-albumin↓ Hm, low C3 dsDNA 1:600 Liver abscess	SCR 0.4	Diffuse membranous changes focal proliferative GN segmental necrotizing, I.F.: IgG, IgM, C3, C1q-deposits 'Immune complex GN'	Prednisone 30 mg/48 h initially, followed by further immunosuppressive agents	SCR 0.9, SLE, controlled severe Aspergillus infection
McClellan <i>et al.</i> 1992 [6]	18, m		SCR↑		Drainage of <i>Staph. aureus</i> abscess, antibiotics	Recovery of renal function
This case	5.5 m	SLE with NS	SCR 0.5	Diffuse proliferative GN, IF: IgA, IgG, IgM, C3, C3d	Steroids, rifampicin, itraconazole	SCR 0.3 P 0.3–0.9 g/m ² /d

P, proteinuria (g/d); Hm, haematuria, microscopic; SCR, serum creatinine (mg/dl); GFR, glomerular filtration rate (ml/min); NS, nephrotic syndrome; GN, glomerulonephritis; ESRD, end-stage renal disease; d, day, I.F., immunofluorescence.

carriers of CGD had clinical features consistent with lupus-like lesions, such as discoid lupus, photosensitivity, or aphthous stomatitis. The serological findings in these carriers were negative with two exceptions: one with discoid lupus and positive ANA-titres [12] and one with clinical symptoms of SLE but without renal manifestations [13]. In another carrier transient glomerulonephritis was noted during childhood [14]. In addition, four CGD patients were reported to have discoid lupus without dsDNA antibodies [15–17].

The pathoanatomical features observed in the six cases of CGD reported with glomerular lesions were variable (Table 2). Besides focal proliferative and sclerotic lesions, diffuse glomerular involvement was observed as in our case. Granulomas of the kidney were noted in only one case [9]. Other forms of renal granulomatous disease seem to be excluded. The presence of diffuse immunoglobulin and complement deposits in kidney or skin biopsies [6,7,10] suggests an immune-complex nephritis. This is supported by rising titres of circulating immune complexes, as were found in another patient [8].

The association of CGD with glomerular lesions and SLE may be the result of an exaggerated inflammatory response observed in this disorder. Due to the defective phagocytes, microbial persistence may lead to chronic antigen stimulation of the immune system. Studies by Sato *et al.* [18] in renal biopsies of patients with IgA nephropathy suggest that phagocytic dysfunction of PMN may cause mesangial deposition of immune complexes. The repeated exposure to antigens from damaged host cells in CGD could result in overproduction of autoantibodies. In addition, impaired clearance of antigens or soluble immune complexes due to overload of the reticuloendothelial system might cause renal damage. The development of autoimmune phenomena including SLE also occurs with other hereditary defects of host defence mechanisms or from acquired immune deficiency syndromes [19–21]. Our hypothesis is supported by animal experiments that showed immune complexes binding to glomerular cells, stimulating superoxide release [22].

The outcome of CGD patients associated with glomerulonephritis varied (Table 2). The case described by van Rhenen *et al.* [7] deteriorated rapidly and reached end-stage renal disease within 4 months but recovered, at least partly, after 7 months on dialysis treatment. A partial recovery was also reported in the other cases except in that of Frifelt *et al.* [9] who died after 15 months on dialysis. The immunosuppressive treatment applied in that case was repeatedly followed by pulmonary infiltrations due to *Aspergillus* sepsis and was therefore discontinued. The case reported by Manzi *et al.* [10], also associated with SLE, was treated with steroids and showed a prolonged course, complicated by multiple *Aspergillus* and other infections involving the CNS; for the last 4 years this patient was without signs of SLE and the proteinuria seems to be well controlled without immunosuppressive therapy (personal communication A. H. Urbach).

We were encouraged to use steroids because their

administration was successful and well tolerated in CGD patients with obstructions of the gastrointestinal or urinary tract secondary to persistent granuloma formation. However, medication has been given in lower doses and for limited time [6,23]. In our case steroid treatment was well tolerated and induced a clinical and serological remission of SLE and renal symptoms, with a decline of proteinuria below 1 g/m²/day and stable GFR. The mild course of intercurrent infections we observed during steroid therapy may be ascribed to the relatively high number of residual cytochrome-b-positive PMN in our patient (3% versus none in most cases of X-linked CGD). Lifelong chemoprophylaxis against infections seems to be important for the outcome [2]. Rifampicin was chosen because co-trimoxazole had previously induced thrombocytopenia; in addition, it may be a potential cause of discoid lupus. Itraconazol was added as a potent oral antifungal agent which is also active against *Aspergillus*. In a recent prospective randomized trial interferon gamma was found to reduce the frequency of severe infections [25,26]. This drug was avoided because of its risk of inducing SLE [27] and previous applications in our case provoked fever.

In conclusion CGD must be regarded as a potential cause of chronic glomerulonephritis. Children and young adults with repeated purulent infections who present with unexplained proteinuria should be screened for this disorder. The combination of CGD with SLE reported here strongly suggests an immune pathogenesis. An optimal treatment schedule needs to be worked out for similar cases.

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